REMARKS

Applicant acknowledges, with appreciation, the Examiner's indication that the Formal Drawings filed on April 16, 2003 are accepted.

The Objections

Title of the Invention

The Examiner objected to the title of the invention as not being descriptive of the claimed invention and contends that a new title is required that is clearly indicative of the invention's claimed subject matter. Applicant has amended the title accordingly.

Claims

The Examiner has objected to claim 10 for improper use of the term "of". Applicant has amended claim 10 to delete the objected-to term.

The Examiner has objected to claim 11 due to the misspelling of the term "initialing". Applicant has amended claim 11, replacing the misspelled term with the word -- initializing --.

Applicant has amended claim 15 to correct a typographical error that resulted in improper dependency. In particular, applicant has amended claim 15 to properly depend from claim 14.

The Examiner has objected to claim 16, due to the inclusion of non-elected subject matter.

Applicant directs the Examiner's attention to MPEP § 809.04, which states that "[w]here the requirement for restriction in an application is predicated upon the non-allowability of generic or other type of linking claims, applicant is entitled to retain in the case claims to the non-elected invention or inventions." Applicant elects to maintain claim 16 herein until the Examiner's final disposition regarding the allowability of generic claims herein.

Finally, applicant has amended claims 1 and 48 to refer to the experimental X-ray diffraction data in the preamble. Support for this amendment can be found, for example, at page 2, lines 8-10 and 19-26; page 12, lines 3-7 and 13-17; page 12, line 26 through page 13, line 2; and page 33, lines 17-27 of the specification. Applicant has also amended the preambles of claims 1 and 48 to recite "parallel" computational means. Support for this amendment can be found, for example, on the entirety of page 23 of the specification. Claims 1 and 48 have also been amended to recite a complex-valued coefficient wherein said coefficient's phase angle is any one of the set of presumed values 0° and 90°. Support for this amendment can be found, for example, at page 18, lines 4-9 and page 23, lines 5-11 of the specification.

As discussed *infra*, applicant has amended claims 1, 2, 41, 42 and 48 in response to the rejection under 35 U.S.C. § 101.

Other informalities

The Examiner has objected to the disclosure, contending that the specification contains incomplete references to citations or figures, in particular, on page 9, lines 8 and 9. Applicant has amended the specification to correct errors and provide missing references to figures. Support for these amendments can be found in the corresponding drawings as originally filed.

Applicant has amended page 34 of the specification to include the subject matter of originally-filed claims 14, 46 and 47.

Finally, applicant has amended the "Brief Description of the Drawings." Support for these amendments can be found in the corresponding drawings as originally filed.

None of the amendments to the specification or claims constitutes new matter.

The Rejections

35 U.S.C. § 101

Claims 1-12, 14, 16-23, 37, 39-45, 47-53, 61 and 62 stand rejected under 35 U.S.C. § 101, as purportedly being

directed to non-statutory algorithm-type subject matter. The
Examiner contends that claimed method for determining the
three-dimensional structure of a molecule of interest is not
statutory subject matter since it lacks any physical steps,
such as displaying said molecule of interest. The Examiner
states that the "critical steps of displaying the molecule [of]
interest would cause the subject matter in its entirety to be a
statutory application."

Applicant has amended claims 1, 2, 41, 42 and 48 to
recite the additional step of outputting the resulting data
structures to an output hardware, including a display device.
Support for this amendment can be found in the specification
at, for example, page 34, lines 12-28, as currently amended to
incorporate the subject matter of originally-filed claims 14,
46 and 47. These amendments obviate the 35 U.S.C. § 101
rejection.

35 U.S.C. § 112, second paragraph

Claims 1-12, 14-23, 37, 39-53, 61 and 62 stand
rejected under 35 U.S.C. 112, second paragraph, as being
indefinite for failing to particularly point out and distinctly
claim the subject matter which applicant regards as the
invention. In particular, the Examiner contends that the term
"becomes" in claims 1 and 48, step (f), causes each claim to be
vague and indefinite, since it is unclear how each spherical
harmonic spherical Bessel ("SHSB") basis function becomes a
Fourier representation. The Examiner contends that it cannot

be determined whether the SHSB function spontaneously becomes a
Fourier representation, or whether some data analysis or data
manipulation is involved. The Examiner further contends that
this language in step (f) causes step (g) to be vague and
indefinite, since it is unclear how the calculation of the
Fourier representation of each SHSB basis function is
accomplished in step (g) when such a step has been achieved in
step (f).

Step (f) of claims 1 and 48 is directed to the
interconversion of a SHSB function to a Fourier (plane wave)
representation *at a particular point within the unit cell*.
Step (g), in the instance wherein the electron density of the
unit cell is described by more than one SHSB function, involves
the calculation of a Fourier representation for the *entire unit
cell*. Therefore, step (f) involves a data manipulation step, a
step which is distinguishable from the calculation of the
Fourier representation of the entire unit cell achieved in step
(g).

The Examiner also asserts that the term "complex-
valued" causes the claims to be vague and indefinite, since it
is unclear what criteria is being used to consider that a
coefficient is "complex-valued", that is whether it pertains to
a complex comprising a receptor and a ligand or refers to the
difficulty of determining the coefficients.

The term "complex-valued" refers to the values of
a_{lmn}, which is defined, at page 11, line 5 of the specification,

as equal to $|a_{lmn}|e^{i\alpha lmn}$. Therefore, the values of a_{lmn} belong to the set of complex numbers, or the set of numbers that may be described by the equation x+iy, where x and y are real numbers, wherein "i" is the imaginary number or square root of -1.

The Examiner also contends that there is no antecedent basis in step (h) of claims 1 and 48 for "experimental x-ray diffraction".

Applicant, as discussed *supra*, has amended the preamble of claims 1 and 48 to recite "experimental X-ray diffraction data," thereby providing antecedent support for that phrase in step (h).

The Examiner also asserts there is insufficient antecedent basis for the claim 2 recitation "diffracting molecule."

Applicant has amended claim 2 to delete the adjective "diffracting" and to recite the three-dimensional model structure as that of a "molecule of interest", in conformity with claim 1.

The Examiner further contends that the term "improvements" renders claims 2 and 9 vague and indefinite, since it is purportedly unclear whether the modeling process or the data generated from the process is being improved.

The term "improvements" as used in claims 2 and 9 refers to the improvement of the three-dimensional model structure data itself.

Lastly, the Examiner contends that the phrase "more often" recited in step (b) of claim 48, purportedly renders the claim vague and indefinite. Claim 48 has been amended to delete the objected-to phrase.

35 U.S.C. § 112, first paragraph

Claims 1-12, 14, 16-23, 37, 39-45, 47-53, 61 and 62 stand rejected under 35 U.S.C. § 112, first paragraph, as being enabling for a method for determining the three-dimensional structure of *Staphylococcal aureus* nuclease, but purportedly not providing enablement for any other molecule. The Examiner contends that protein crystallization is an unpredictable art, a trial and error process that, coupled with applicant's disclosure, purportedly provides too little guidance to the skilled artisan to make and use the claimed invention without undue experimentation. Applicant traverses, in view of the foregoing claim amendments and the following remarks.

Although the methods of the claimed invention are applied to X-ray diffraction data sets of a given molecule of interest, the purported unpredictability of protein crystallization is not inherent therein. The claimed invention is directed to methods that may be applied to any and all pre-

existent X-ray diffraction data sets, irrespective of the manner by which they are derived.

Claims 1-12, 14, 16-23, 37, 39-45, 47-53, 61 and 62 also stand rejected under 35 U.S.C. § 112, first paragraph, as being enabling for the determination of the three-dimensional structure of a *Staphylococcal aureus* nuclease using only those equations (1-12) as disclosed on pages 10-14 of the application. Applicant traverses.

Applicant draws the Examiner's attention to MPEP § 2164.08, wherein it is stated that although the specification must teach those skilled in the art how to make and use the full scope of the invention without "undue experimentation", the scope of the enablement must only bear a "reasonable correlation" to the scope of the claims (see, for instance, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)). In particular, "[i]n cases involving predictable factors...a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws." *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24. Applicant's disclosure teaches one of skill in the art means by which to mathematically generate three-dimensional representations of electron density derived from X-ray diffraction data. Given such disclosure, the skilled artisan would be able to practice the full scope of the present claims. The Examiner has pointed to no scientific evidence to the

contrary. In the absence of such evidence, enablement of applicant's claims must be accepted.

35 U.S.C. § 102(b)

Claims 1-12, 14-23, 37, 39-53, 61 and 62 stand rejected under 35 U.S.C. § 102(b), as being anticipated by Friedman, J.M. Comput. Chem. Vol. 23, No. 1, pp. 9-23 (January 1999)(hereinafter "Friedman").

Applicant notes that Friedman discloses a single means by which the skilled artisan would derive the complex values for each index l, m, and n. This method involves the calculation of 72 values of α_{lmn} at 5 degree intervals, the completion of which requires 9 weeks. In contrast, applicant teaches a novel method of calculating the complex values of α_{lmn} by making the determination at 0° and 90° and using the two values and an arc tangent function to derive the α_{lmn} value, the completion of which takes less than 1 week. This improvement allows for the determination of the amplitude and phase in just two calculations. In contrast, Friedman teaches the separate determination of amplitude and phase. Applicant has amended step (g) of both claims 1 and 48 to recite the calculation of the scale factors and correlation coefficients of the phase angle at 0° and 90°. Furthermore, Friedman does not disclose applicant's novel parallelization scheme, an exemplary embodiment of which is taught in the instant application as reducing the time for determining α_{lmn} coefficients to 18 hours when used in combination with applicant's calculation of two

presumed angles for the spherical harmonic spherical Bessel coefficients for F_{solo} and F_{accum}. This reduction of time, as compared with the technique of Friedman, is achieved even while using fewer processors. Applicant has amended claims 1 and 48 to recite a method of parallel computation. Friedman does not teach the skilled artisan how to achieve the results of applicant's invention with the same accuracy or the same speed that characterizes the methods of the instant claims.

The Examiner contends that Friedman discloses a method for interconverting three-dimensional molecular spatial information with spherical harmonic-Bessel representation and non-centrosymmetric crystalline arrays, thereby anticipating claims 37 and 49. In view of the foregoing amendments and remarks, applicant disagrees.

Friedman does not anticipate the methods of claims 37 and 49. One of skill in the art could not use the methodology of Friedman to determine α_{lmn} with the accuracy and speed of the present invention and therefore could not describe a single asymmetric object in space by a three-dimensional SHSB expansion in the manner taught by applicant. Therefore, Friedman does not anticipate claim 37 or claim 49.

The Examiner also asserts that Friedman anticipates step (a) in claims 1 and 48 as well as claims 3, 16 and 50 by testing the method described therein with a few macromolecular crystals of known structure.

Friedman does not demonstrate parallel computation of α_{lmn} condensing determination of phase and amplitude into just two calculations. Therefore, application of Friedman's method to macromolecular crystals of known structure does not anticipate any of claims 1, 3, 16, 48 or 50.

The Examiner further asserts that claims 4 and 51 are anticipated by Friedman, insofar as that document discloses exhaustive searches to find the positional and rotational orientation of a known molecule in a new crystalline packing arrangement based upon a measured X-ray diffraction pattern with the Fourier phase information associated with said diffraction pattern unknown.

Friedman's exhaustive search schemes do not compute the scale factors and correlation coefficients for α_{lmn} in the same manner as the current invention nor do they employ applicant's parallelization method. Therefore, the search methods of Friedman do not anticipate claim 4 or 51.

The Examiner further contends that step (b) in claims 1 and 48 and step (k) in claim 2 are anticipated by Friedman's disclosure that the method based upon orthogonal basis functions allows for two of the final three rotational degrees of freedom to be calculated by FFT and the final rotation calculated quickly by multiplying the spherical harmonic coefficients by a matrix as well as the disclosure of the use of DOCK for modeling the docking of ligands into a protein. The Examiner also contends that claims 1 and 48, in particular

step (c), are anticipated by Friedman's disclosure of a
resolution limit of 3.0 Å in the evaluation of the FFTs. And
the Examiner asserts that claims 1 and 48, in particular steps
(d) and (g), and claim 6 are anticipated by Friedman's
disclosure of the selection of two arbitrary geometric
parameters, radius and position, are determined for the unit
cell lengths and angles in terms of the Fourier expansion. The
Examiner further asserts that step (e) of claims 1 and 48 are
anticipated by Friedman, insofar as that document discloses a
prescreening step that reduces the number of translation points
that need to be considered. The Examiner contends that step
(f) of claims 1 and 48 is anticipated by Friedman's disclosure
of calculated interconversion between the spherical harmonic-
Bessel representation and the Fourier representation. And the
Examiner contends that claims 1 and 48, in particular steps
(h), (i) and (j), as well as claims 7-9, 11 and 39-42 are
anticipated by Friedman's disclosure that complex-valued
coefficients, Fourier summations, and indices are calculated
according to equations 3-5. The Examiner also contends that
claim 2, in particular step (1), is anticipated by Friedman's
recitation of a method designed to provide functional maxima or
minima for each of the energy terms calculated.

As well accepted, "[a] claim is anticipated only if
each and every element as set forth in the claim is found,
either expressly or inherently described, in a single prior art
reference." (*Verdegaal Bros. v. Union Oil Co. of California*,
814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)).

Because <u>Friedman</u> does not disclose every element set forth in claims 1, 2 and 48, it does not anticipate those claims. Nor can <u>Friedman</u> be made to do so via selection of individual elements of the claims and piecemeal comparison thereto. The teaching of <u>Friedman</u> must be regarded as a whole. <u>Friedman</u> does not disclose applicant's parallelization method, nor does it disclose the computation of the amplitude and phase of α_{lmn} in a calculation sampling only two phase angles. Therefore, <u>Friedman</u> does not anticipate any of claims 1, 2 or 48.

Claim 10 stands rejected as being anticipated by <u>Friedman</u>'s disclosure that the value of zero is considered in the aforementioned calculations. Claim 5 stands rejected as being anticipated by <u>Friedman</u>'s disclosure of a method for non-overlapping spherical expansion zones. Claim 12 stands rejected as being anticipated by <u>Friedman</u>'s recitation of equations 6-8, which are used for converting from a series of spherical harmonic coefficients to one of Fourier structure factor amplitudes and phases.

<u>Friedman</u> does not anticipate each element of any of claims 5, 10 or 12, since <u>Friedman</u> does not teach applicant's parallelization scheme or its truncated phase angle search allowing for calculation of amplitude and phase in just two calculations.

Lastly, claims 14, 15, 17-23, 43-47, 52, 53, 61 and 62 stand rejected, in view of <u>Friedman</u>'s recitation of the use

of a DEC-alpha-4000 workstation for data input and output and model display.

Friedman does not anticipate each element of claims 14, 15, 17-23, 43-47, 52, 53, 61 or 62, since Friedman does not teach applicant's parallelization scheme nor its truncated phase angle search allowing for calculation of amplitude and phase in just two calculations.
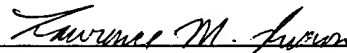
In view of these essential differences between applicant's methods and those of Friedman, that publication fails to anticipate the claims of the pending application. Accordingly, the claim rejections under 35 U.S.C. § 102(b) should be withdrawn.

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CONCLUSION

Applicant respectfully requests that the Examiner consider the foregoing amendments and remarks, and pass this application to issue.

Respectfully submitted,

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